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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,677	10/22/2003	Neil M. Wolfman	08702.0093-00000	2405

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EXAMINER

DUTT, ADITI

ART UNIT	PAPER NUMBER
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1649

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/689,677	Applicant(s) WOLFMAN ET AL.	
	Examiner Aditi Dutt	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 10-17, 23-26 and 29-39 is/are pending in the application.
- 4a) Of the above claim(s) 24-26, 38-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 10-17, 23 and 29-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-5, 10-17, 23-26 and 29-39 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/21/06, 8/21/06</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Aditi Dutt.

Status of Claims

1. The amendment filed on 21 August 2006 has been entered into the record and has been fully considered. Claims 1, 3-5, 25-26 and 29-31 are amended.
2. Claims 6-9, 18-22, 24 and 27-28 are canceled. New claims 36-39 have been added.
3. Claims 1-5, 10-17, 23 and 29-37, drawn to a method for ameliorating a symptom of at least one degenerative disorder associated with the growth and differentiation factor-8 (GDF-8) are under consideration in the instant application. Applicant's previous election (response of 06 March 2006) of muscular dystrophy as the species will be considered for examination. Applicant's arguments traversing the restriction requirement for claims 29-35 and the withdrawal of these claims by the previous Examiner are found to be persuasive, because after further consideration these claims recite further limitations within the scope of the elected invention. Therefore, claims 29-35 will be rejoined and examined along with the other pending claims in the instant specification.
4. Claims 25-26 and 38-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention and/or

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species, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 06 March 2006.

5. The text of any section of 35 U.S.C. not reiterated in this office action can be found in a previous office action.

Information Disclosure Statement

The duplicate information disclosure statement submitted on 21 August 2006 has been crossed off by the Examiner. The references have been considered.

Claim Objections

6. Claims 1, 12-17 objected to because of the following informalities:
Regarding claims 1, 12-17, acronyms "GDF-8", and "ActRIIB" recited should be spelled out in all independent claims for clarity.
Appropriate correction is required.

Claim rejections maintained/new grounds of rejection

Claim Rejections - 35 USC § 112

7. Claims 1-5, 10-17, 23, 29-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the stimulation of increased muscle mass via administration of an ActRIIB-Fc (type II activin receptor B) fusion protein as exemplified in Example 9 (pages 46-47), does not reasonably provide enablement for ameliorating any symptom of a degenerative disorder of muscle, by administering a generic breadth of molecules as directed to peptides with at is at least 95% to 99% identity to amino acids 23 to 138 of

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SEQ ID NO: 3, capable of binding to GDF-8 and an Fc portion of an antibody.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 1-5, 10-17 and 23, at page 3-7 of the previous office action (19 May 2006).

8. Applicant's arguments (21 August 2006), as they pertain to the rejection, have been fully considered but are not deemed to be persuasive for the following reasons.
9. (A) Applicant argues that because "ActRIIB fusion protein with 95% identity to amino acids 23 to 138 of SEQ ID NO: 3 maintains its ability to bind to GDF-8", undue experimentation will not be necessary of the skilled artisan to use the above variants for binding assays. Applicant cites case law with respect to these issues. Applicant also asserts that based on the disclosure in the specification and the knowledge of those skilled in the art, any artisan would be able to make and use the claimed ActRIIB variants.
10. Applicant's arguments filed on 21 August 2006 have been fully considered but they are not persuasive. As stated previously based on the state of the art, one or more amino acid deletions, insertions or substitutions including truncations result in unpredictable effects in the resulting biological molecule, its biological functions, the ability to bind and/or exhibit similar activity. The examiner takes no issue with case law.

11. Specifically, as discussed in the previous Office Action, certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Furthermore, recitation of the phrase "..... an ActRIIB fusion polypeptide, comprising (a) an amino acid sequence that is at least 95%, 97%, 98% or 99%

identical to amino acids 23 to 138 of SEQ ID NO: 3 and is capable of binding to GDF-8" in the claims is not adequate to describe the ActRIIB polypeptide variants that have at least 95%, 97%, 98% and 99% homology to the ActRIIB polypeptide, since there is no physiological activity associated with these variants. Undue experimentation would be required by the skilled artisan to determine such.

12. (B) Applicant further argues that because "the extracellular domain of activin receptor type II is 54% identical to the extracellular domain of activin receptor type II B" based on their cited reference, "residues or fragments of ActRIIB are highly conserved" and exhibits potential GDF-8 binding activity.

13. Applicant's arguments have been fully considered but they are not persuasive. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality,

resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, *Nature Biotechnology* 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, *Trends in Genetics* 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, *Trends in Genetics* 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

14. Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polypeptides to make biologically active ActRIIB variants without resorting to undue experimentation to determine what the specific biological activities of the ActRIIB variants are.

15. (C) Applicant argues that a 'mdx murine model' showed increased muscle mass and strength (Bogdanovich et al., 2002, page 11). Applicant further argues that the ActRIIB fusion polypeptide inhibited GDF-8 and increased muscle mass in an in vivo (C57B6/SCID) mouse model (Example 9), thereby asserting that the results observed in the mouse model "correlates with that same function in humans". Furthermore, Applicant argues that the Fabb article cited by the Examiner is directed to gene therapy that is different from protein therapeutics.
16. Applicant's arguments have been fully considered but they are not persuasive. As discussed in the previous office action, the mdx mouse model taught in the Bogdanovich reference is recognized to be an appropriate genetic and biochemical model for a degenerative disorder such as Duchenne muscular dystrophy (DMD) (Han et al., Muscle Nerve 33: 208-214, 2006; Collins and Morgan, Int J. Exp Pathol. 84: 165-172, 2003). Based on electromyographic studies in mdx and wild-type C57 mice, Han et al., showed that motor unit action potentials were normal in wild type C57 muscles, versus abnormal spontaneous potentials and complex repetitive discharges in mdx mice, a finding comparable to that observed in muscles from boys with DMD (page 211, Figures 2 and 3; page 212, column 2, para 3). Applicant's arguments with respect to the Fabb article is fully considered but not found persuasive, as the previous Examiner merely utilized Fabb to emphasize that an appropriate animal model is essential for the predictability of findings in degenerative disorders such as muscular dystrophy in humans.

17. Furthermore, as exemplified by Example 9 of the instant specification and Applicant's arguments at page 11 of the response, the ActRIIB fusion protein stimulates increased muscle mass in vivo. The specification provides no methods or working examples to indicate that all possible symptoms of all possible degenerative disorders of muscle can be ameliorated by administration of an ActRIIB fusion protein as required by the claims. Undue experimentation would be required of the skilled artisan to determine such.
18. Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of variants of ActRIIB fusion peptide, and to administer the construct for therapeutic use to treat any degenerative disorder of muscle; the lack of direction/guidance presented in the specification regarding the same; the complex nature of the invention; the unpredictability of administering the fusion peptide in vivo and the state of the prior art which establishes the utilization of the animal models to study/treat degenerative disorders; and the breadth of the claims which fail to recite any structural or functional limitations - undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Written Description

19. Claims 1-5, 10-17, 23, 29-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth for claims 1-5, 10-17 and 23, at page 7-9 of the previous office action (19 May 2006).

20. Applicant argues that the recited polypeptides in the instant specification exceeds the written description requirement as stated in USPTO's Written Description Guidelines (Example 14), because the claims related to the polypeptide satisfy structural and functional limitations (95-99% identity and having GDF-8 binding activity), required for written description compliance. Applicant also argues that the specification provides both structure and physical properties of the claimed genus.

21. Applicant's arguments have been fully considered but they are not persuasive. As explained in the previous office action, the claims recite polypeptides comprising fragments and variants with varying lengths and amino acid composition. Furthermore, the functional limitation "binding to GDF-8" recited in claim 1, does not sufficiently describe the functional characteristic of the genus of GDF-8 variants.

22. With the exception of the ActRIIB peptide sequences comprising amino acids 23-138 of SEQ ID NO: 3, and the ActRIIB fusion polypeptide comprising amino acids 19-144 of SEQ ID NO: 1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of

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the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *polypeptide itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

23. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

24. Therefore, only nucleic acids encoding the ActRIIB peptide and the ActRIIB fusion peptide comprising the amino acid sequence of SEQ ID NO: 3, 1 respectively, and methods of increasing muscle mass in vivo using the ActRIIB fusion peptide, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

25. Furthermore, even if the written description issue for GDF-8 variants is overcome, claims 1-3, 10-17, 23, 29-35 would remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

26. The specification teaches that ActRIIB is a type II activin receptor that also binds to GDF-8 and inhibits its activity in vivo and in vitro (page 5, para 0014).

The specification also teaches that GDF-8 activity refers to the growth-regulatory or morphogenetic activities associated with GDF-8, such as a negative regulation of skeletal muscle, production of creatine kinase, stimulation of myoblast proliferation and modulation of differentiation to adipocytes (page 12, para 0037). Furthermore, the specification teaches that GDF-8 is associated with a number of neuromuscular disorders such as muscular dystrophy, amyotrophic lateral sclerosis, muscle atrophy, carpal tunnel syndrome and other muscle wasting syndromes (page 9, para 0029). However, the brief description in the specification of one example of increasing skeletal muscle weights in C57B6/SCID mice, is not adequate written description of an entire genus of methods encompassing a genus of symptoms for a genus of muscle degenerative disorders associated with GDF-8. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. However, in this case, the specification has not shown adequate identifying characteristics of the claimed genres of degenerative disorder and symptom to be ameliorated.

27. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing

date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

28. The skilled artisan cannot envision the genus of degenerative disorders of muscle and genus of symptoms to be ameliorated, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

29. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

30. Therefore, only methods of increasing skeletal muscle mass in muscular dystrophy, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

31. Claims 1-5, 10-17, 23, 29-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
32. The term "stringent" in claim 23 is a relative term which renders the claim indefinite. The term "stringent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Stringency is relative, and the art does not recognize a single set of conditions as stringent. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions consisting of **A** X SSC and **B** % SDS at **C**°C"), the claim fails to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.
33. The term "GDF-8 activity" in claims 1-5, 10-17, 23, 29-37 is a relative term which renders the claim indefinite. The term "GDF-8 activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what physiological

functions/activities are encompassed by this phrase (i.e. production of muscle-specific enzymes, stimulate myoblast proliferation, differentiation to adipocytes)

Conclusion

34. No claims are allowed.
35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Tsuchida K., Curr Drug Targets Immune Endocr Metabol Disord. 4(2):157-66, 2004

(Reference showing GDF-8 for drug targets)

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.
37. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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38. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
October 20, 2006


JANET L. ANDRES
SUPERVISORY PATENT EXAMINER